Sulfamic acid functionalised magnetic nanoparticles: an efficient solid acid for the multicomponent condensations

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Sulfamic acid-functionalised magnetic nanoparticles have been synthesised and used as efficient heterogeneous solid acid catalysts for the condensation of aromatic aldehydes with 2-naphthol and amides (or carbamates) via three-component reactions under solvent-free conditions at 80 °C. Quantitative conversion of the reactants is achieved under mild conditions. Recovery of the catalyst is easily achieved by 'magnetic decantation'. The supported catalyst is reused four times without any significant degradation in catalytic activity.

Keywords: sulfamic acid, amidoalkyl naphthols, heterogeneous catalyst, magnetic decantation, solvent-free conditions, multicomponent reactions, nanoparticles

In synthetic organic chemistry, multicomponent reactions (MCRs) have gained considerable popularity in recent years due to their flexible, convergent, and atom-efficient nature. The MCRs are an ideal synthetic tool to generate multiple molecular scaffolds and to increase structural and skeletal diversity.[1]

Surface functionalised iron oxide magnetic nanoparticles (MNPs) have emerged as feasible substitutes to conventional materials as robust, active, high-surface-area catalyst supports for one-pot MCR condensations.[2–10] In view of their nano-size, the contact between reactants and catalyst increases dramatically thus mimicking the homogeneous catalysts.[11] The magnetic nature of these particles allows for easy recovery and recycling of the catalysts by an external magnetic field, which may optimise operational cost and enhance product purity.[12] Consequently, there has been considerable interest in the development of stable, reusable, and highly active solid acids[13] as environmentally benign replacements for their homogeneous counterparts.

During the last few years, sulfamic acid (NH_2SO_3H, SA), a dry nonhygroscopic, nonvolatile, and odourless solid has been considered as an efficient heterogeneous catalyst substitute for conventional acidic catalysts.[14–20] In this study, we report sulfamic acid-functionalised magnetic nanoparticles (SA-MNPs) as efficient heterogeneous catalysts for the one-pot synthesis of amido-alkyl naphthols (AANs) and carbamato-alkyl naphthols (CANs) via three-component couplings of aldehydes, amides (or carbamates) and 2-naphthol in solvent-free conditions.

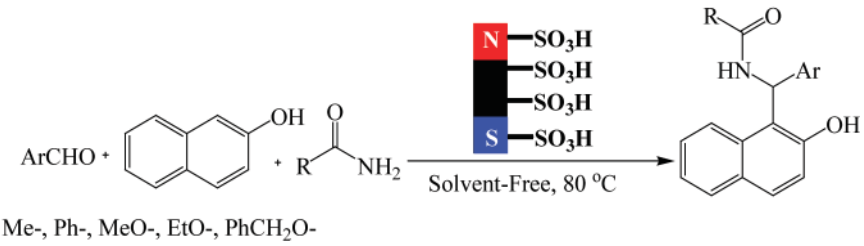
AANs and CANs as precursors have been used for preparation of a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[21] The hypotensive and bradycardiac effects of these compounds have been evaluated.[22] The intramolecular cyclisation of AANs by Vilsmeier reagents produce 1,3-oxazines.[23] The synthesis of 1,3-oxazines has attracted attention because of their potential as antibiotics,[22] anti-hypertensive,[24] and potent anti-rheumatic agents.[25] In continuation of our research on the application of heterogeneous catalysts in organic reactions,[26–31] we have employed SA-MNPs in preparation of AAN and CANs (Scheme 1).

Results and discussion

Our initial study focused on the development of the optimal reaction conditions for this transformation. To determine the best weight of the catalyst and temperature, as shown in Table 1, syntheses were carried out in the presence of different amounts of catalyst and at different temperatures. Initially, the reaction was studied without any catalyst at 120 °C but only afforded a poor yield (14%) of the final product (Table 1, entry 1). Table 1 shows a remarkable increase in yields according to the increase in the quantity of catalyst and temperature.

In order to use the minimum mass of the catalyst and temperature, we have been limited to 20 mg mol^{-1} of catalyst at 80 °C for the continuation of this study to determine optimum conditions (Table 1, entry 12) for synthesis of a variety of substrates. The results are summarised in Table 2.

As can be seen from Table 2, electronic effects and the nature of the substituent on the aromatic rings showed clear effects in terms of reaction time under the reaction conditions mentioned. In all of the cases, the corresponding AANs and CANs were obtained in good to excellent yields. Aromatic aldehydes substituted by electron-donating groups (EDG) (Table 2, entries **j–o**) require a longer reaction time than those of electron-withdrawing groups (EWG) (Table 2, entries **b–h**). While *meta*- and *para*-substituted aldehydes gave good results, *ortho*-substituted aldehydes require a longer time because of the steric effects. We also used benzamide and methyl, ethyl or benzyl carbamates instead of acetamide in the mentioned reaction and the corresponding products were obtained in good to excellent yield with short reaction times. Under the same conditions, this reaction did not proceed when heterocyclic 2-pyridinecarbaldehyde (Table 2, entry **i**) and aliphatic aldehydes such as propionaldehyde or heptaldehyde (Table 2, entries **p**, **q**) were used as the starting material.



Scheme 1 Preparation of AANs and CANs.

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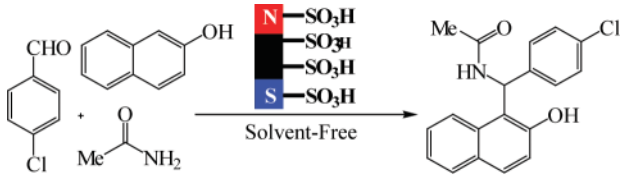
Table 1 Catalyst and temperature screening for the synthesis of **9**[a,b]



Entry	Temperature/°C	Catalyst/mg	Yield of 9/%[c]
1	100	–	14
2	35	200	68
3	50	200	76
4	65	200	82
5	80	200	91
6	100	200	93
7	120	200	93
8	80	150	92
9	80	100	90
10	80	50	91
11	80	30	92
12	**80**	**20**	**93**
13	80	10	88
14	80	5	81
15	80	1	73

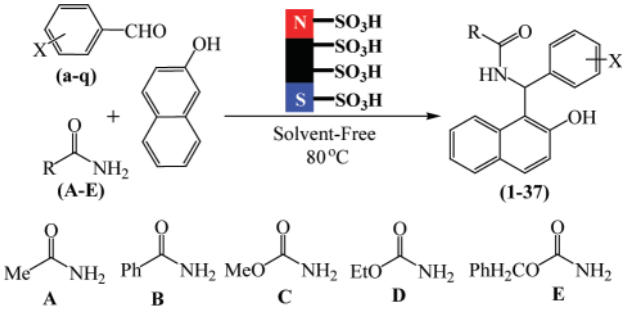
[a]All reactions were conducted with 4-chlorobenzaldehyde (1 mmol), 2-naphthol (1 mmol), acetamide (1.2 mmol) and SA-MNPs in solvent-free conditions. [b]The time of all reactions is 1 h. [c]Isolated yields.

As reported in the literature,[32] the reaction of 2-naphthol with aromatic aldehydes in the presence of an acid catalyst is known to give *ortho*-quinone methides (*o*-QMs) as highly reactive and ephemeral intermediates. The same *o*-QMs, generated *in-situ*, have been reacted with amides to form the desired derivatives. A reasonable explanation for this result can be given by considering the nucleophilic addition to *o*-QM intermediates favourable via conjugate addition on to the α, β-unsaturated carbonyl group that aromatises to the naphthalene ring of this intermediate. The EWD substitution on a benzaldehyde in *o*-QM intermediates increases the rate of 1,4-nucleophilic addition reaction because the alkene LUMO is at lower energy in the neighbouring withdrawing groups than in the case of an EDG example.[26] The reactions of aliphatic aldehydes (Table 2, entries **p, q**) instead of aromatic aldehydes were not completed and only gave the desired products with a low yield as well as observed also with the known catalysts, such as $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[33] *p*-TSA,[34] and cation-exchange resins,[35] probably due to the lower stability of *o*-QMs from aliphatic aldehydes.

Efficiency and recovery are the key factors which limit applications of catalysts in synthetic chemistry and industrial processes. The recycling of SA-MNPs catalyst was then investigated. After each reaction, dichloromethane (5 mL) was added to the reaction mixture and an external magnetic field was applied on the outer surface of the glass reaction containing the SA-MNPs using a permanent magnet. While the external magnet held the SA-MNPs stationary inside the vessel, the reaction solution was easily decanted and separated from the catalyst (Fig. 1).

A heterogeneous catalyst is more interesting when it can be re-used. For this purpose, the synthesis of **9** was carried out using fresh and recovered SA-MNPs catalyst for a four-cycle run. The recovered catalyst was washed with acetone, dried at 100 °C and was reused. The obtained yields after the four-cycle runs is almost unchanged (92, 90, 86 and 83%) which demonstrates that SA-MNPs can be easily recovered and re-used without any loss of their activity.

Table 2 Synthesis of amidoalkyl naphthol drivatives catalysed by SA-MNPs under solvent free conditions[a]



Entry	X	R	Product	Time /min	Yield /%[a]	Ref.
a	H	**A**	**1**	5	90	26, 32
		B	**2**	3	88	30
		C	**3**	10	82	29
		D	**4**	10	83	—
		E	**5**	15	80	29
b	2-Cl	**A**	**6**	8	84	26
		C	**7**	12	82	36
		E	**8**	15	79	29
c	4-Cl	**A**	**9**	3	93	26, 32
		B	**10**	3	90	30
		C	**11**	8	86	29
		D	**12**	10	82	—
d	2,4-Cl	**A**	**13**	3	91	26, 32
		C	**14**	9	89	29
e	2-NO_2	**A**	**15**	5	85	26, 32
f	3-NO_2	**A**	**16**	2	93	26, 32
		B	**17**	2	94	30
		C	**18**	4	87	29
g	4-NO_2	**A**	**19**	2	91	26, 32
		C	**20**	5	86	29
		D	**21**	5	81	—
h	4-CN	**A**	**22**	3	85	37
		B	**23**	3	88	37
		C	**24**	8	80	—
		E	**25**	14	75	—
i	2-pyridine	**A**	**26**	30	-	—
j	2,4-OMe	**D**	**27**	12	77	—
k	2,5-OMe	**C**	**28**	15	81	29
l	3,4-OMe	**A**	**29**	15	80	26, 32
m	4-Me	**A**	**30**	20	73	26
		B	**31**	20	72	30
n	4-OMe	**A**	**32**	35	65	26, 32
o	3-OMe	**A**	**33**	15	86	26
		C	**34**	20	83	—
		E	**35**	30	80	29
p	ethyl	**A**	**36**	60	trace	—
q	n-hexyl	**A**	**37**	60	trace	—

[a]Yields refer to the isolated pure products. The reaction was carried out under thermal solvent-free conditions in an oil bath at 80 °C.

A comparison for the efficiency of the catalytic activity of SA-MNPs with several previous methods is presented in Table 3. The results show that this method is superior to some of the earlier methods in terms of yields and reaction times.

In conclusion, we have developed a simple, efficient, and green methodology for the synthesis of AANs and CANs using sulfamic acid magnetic nanoparticles (SA-MNPs) under solvent-free conditions at 80 °C. The simple experimental

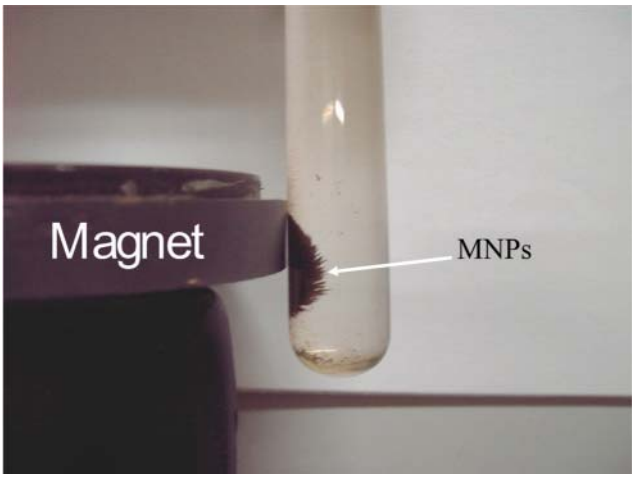


Fig. 1 The attention of magnetic nanoparticles (MNPs) suspended in water by a conventional magnet in about 5 min.

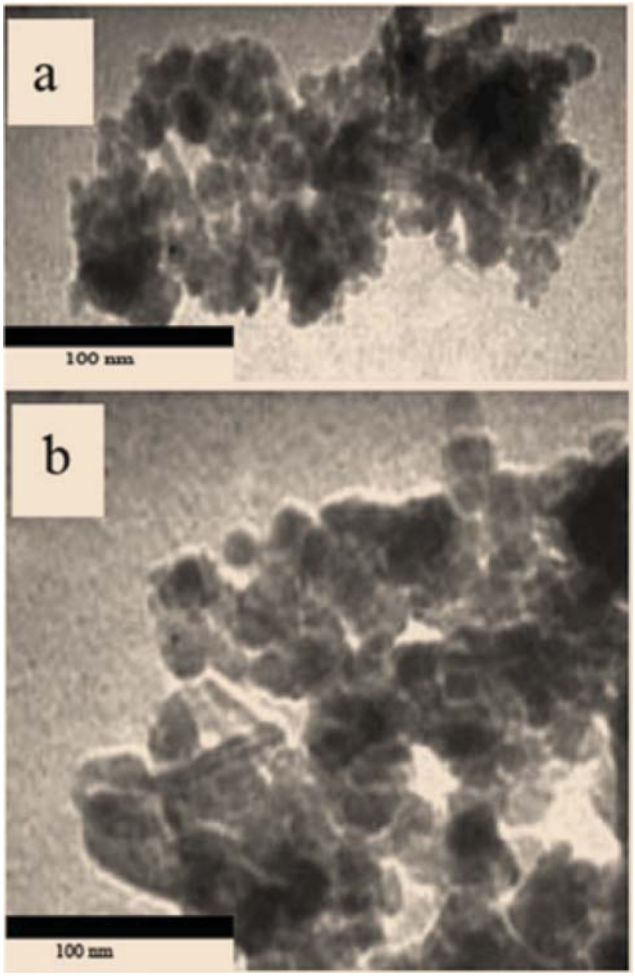


Fig. 2 TEM micrograph of the unfunctionalized (a) and amino-functionalised (b) magnetic nanoparticles.

procedure, solvent-free reaction conditions, good yields, short time reaction and utilisation of an efficient, easily recoverable and reusable catalyst are the advantages of the present method.

Experimental

Sulfamic acid-functionalised magnetic nanoparticles (SA-MNPs) were produced according to a reported procedure.[20]

Table 3 Comparison of catalytic activity of SA-MNPs with several known catalysts[a]

Entry	Catalyst	Conditions	Time	Yield /%	Ref.
1	$Ce(SO_4)_2$	MeCN, Reflux, 85 °C	36 h	72	32
2	I_2	Solvent-free, 125 °C	4.5 h	87	38
3	K-10 clay	Solvent-free, 125 °C	1.5 h	89	39
4	$Fe(HSO_4)_3$	Solvent-free, 85 °C	50 min	93	27
5	$FeCl_3.SiO_2$	Solvent-free, 120 °C	11 min	86	28
6	SA-MNPs	Solvent-free, 80 °C	5 min	90	This work

[a]Reaction conditions: benzaldehyde (1 mmol), 2-naphthol (1 mmol), acetamide (1.2 mmol).

Synthesis of N-((4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl) acetamide **(9)**

A mixture of a 4-chlorobenzaldehyde (1 mmol), 2-naphthol (1 mmol), acetamide (1.2 mmol) and 20 mg of sulfamic acid-functionalised magnetic nanoparticles (SA-MNPs) as catalyst was vigorously stirred at 80 °C for the specific time (3 min). The end of the reaction was monitored by TLC. After completion, the mixture reaction was diluted by dichloromethane (5 mL); then the catalytic system was removed by an external magnet and reused as such for the next experiment. The organic layer was washed with aqueous solution of 10% $NaHCO_3$ and water, dried with Na_2SO_4 and concentrated to give the crude products. Consequently the desired AAN was purified by a recrystallisation procedure using aqueous EtOH (15%); yield: 93%; m.p. 222–224 °C (lit.[26] 223–225 °C); ^{1}H NMR (DMSO-d_6): δ = 1.96 (s, 3H), 7.05 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 1H), 7.19 (m, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.73 (m, 3H), 8.42 (d, J = 8.6 Hz, 1H), 10.09 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ = 20.6, 23.1, 48.1, 118.9, 119.0, 123.0, 126.9, 128.9, 128.4, 129.1, 129.1, 130.0, 131.2, 132.7, 142.3, 153.7, 169.9 ppm.

Electronic Supplementary Information

The general procedure, spectral data of representative unknown AANs and CANs and copies of FT-IR, ^{1}H and ^{13}C NMR and mass spectra for all unknown compounds are given in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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